IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

Applicant: **Meade et al.** Art Unit No.: **1632**

Application No.: **10/081,400** Examiner: **Joseph T. Woitach**

Filed: **February 20, 2002**

For: **ERYTHROPOIETIN ANALOG-HUMAN SERUM ALBUMIN FUSION**

Attorney Docket Number: **GTC-6D**

Mail Stop AF
Commissioner for Patents
P.O. Box 1450
Alexandria, VA 22313-1450

REPLY/AMENDMENT AFTER FINAL

Dear Sir,

This reply is being filed in response to the Office Action mailed September 19, 2005 in connection with the above-identified patent application. Upon review of the specification and claims it was found that the nucleotide sequence disclosure contained in this application did not comply with the requirements for such a disclosure as set forth in 37 C.F.R. 1.821-1.825. No new matter is entered. As such, Applicant respectfully requests that the above-identified application be amended as follows:

Amendments to the Specification are reflected on page **2** of this paper.

Amendments to the Claims begin on page **4** of this paper.

Remarks begin on page **7** of this paper.

CERTIFICATE OF MAILING UNDER 37 CFR 1.8

I hereby certify that this correspondence is being deposited on 9/29/05 with the United States Postal Service as first class mail with sufficient postage on the date indicated above and is addressed to: Mail Stop AF, Commissioner for Patents, P.O. Box 1450, Alexandria, VA 22313-1450.

Dawn C. Greenaway

Dawn C. Greenaway

IN THE SPECIFICATION:

Please amend the Specification as follows:

Please replace page 3 of the specification with the page attached hereto. Both a clean version of the amended page, as well as a marked up version are submitted herewith as per 37 CFR 1.125.

acids in the peptide linker is selected from the group consisting of (Gly, Ser, Asn, Thr and Ala; the peptide linker includes a Gly-Ser element.

In a preferred embodiment, the fusion protein includes a peptide linker and the peptide linker includes a sequence having the formula (Ser-Gly-G1y-G1y-G1y)y (SEQ. ID 1) wherein y is 1, 2,3, 4, 5, 6,7, or 8. Preferably, the peptide linker includes a sequence having the formula $(Ser\text{-}Gly\text{-}Gly\text{-}Gly\text{-}Gly)_3$ (SEQ. ID 1). Preferably, the peptide linker includes a sequence having the formula $((Ser\text{-}Gly\text{-}Gly\text{-}Gly\text{-}Gly_4\text{-}Ser\text{-}Pro)$ (SEQ. ID 3).

In a preferred embodiment, the fusion protein includes a peptide linker and the peptide linker includes a sequence having the formula (Ser-Ser-Ser-Ser-Gly)y (SEQ. ID 5 [[4]]) wherein y is 1,2, 3, 4, 5,6, 7, or 8. Preferably, the peptide linker includes a sequence having the formula $((Ser\text{-}Ser\text{-}Ser\text{-}Ser\text{-}Gly)_3\text{-}Ser\text{-}Pro)$ (SEQ. ID 4).

In another aspect, the invention features, an EPOa-hSA fusion protein wherein the EPOa includes amino acid residues G1n24, G1n38, G1n83 and A1a126.

In a preferred embodiment the EPOa is G1n24, G[[0]]1n38, Gln83, A1a126 EPO (i.e., only amino acids 24, 38, 83, and 126 differ from wild type).

In another aspect, the invention features, an EPOa-hSA fusion protein which includes from left to right, an EPOa which includes amino acid residues G1n24, Gln38, G1n83 and Ala126, a peptide linker, e.g., a peptide linker having the formula $((Ser\text{-}Gly\text{-}Gly\text{-}GIy\text{-}Gly)_4\text{-}Ser\text{-}Pro)$ (SEQ. ID 3), and human serum albumin.

In a preferred embodiment the EPOa is G1n24, G1n38, G1n83, A1a126 EPO.

In a preferred embodiment the fusion protein is from left to right, G1n24, G1n38, Gln83, Ala126 EPO, a peptide linker having the formula $((Ser\text{-}Gly\text{-}Gly\text{-}Gly\text{-}Gly)_4\text{-}Ser\text{-}Pro)$ (SEQ. ID 3), and human serum albumin.

In another aspect, the invention features, an EPOa-hSA fusion protein which includes, from left to right, human serum albumin, a peptide linker, e.g., a peptide linker having the formula $((Ser\text{-}Gly\text{-}Gly\text{-}Gly\text{-}Gly)_{34}\text{-}Ser\text{-}Pro)$ (SEQ. ID 3), and an EPOa which includes amino acid residues G1n24, G1n38, G1n83 and Ala126.

In a preferred embodiment the EPOa is G1n24, G1n38, Gln83, Ala126 EPO.

In a preferred embodiment the fusion protein is from left to right, human serum albumin, a peptide linker having the formula $((Ser\text{-}Gly\text{-}G1y\text{-}GIy\text{-}Gly)_4\text{-}Ser\text{-}Pro)$ (SEQ. ID 3), and Gln24, Gln38, G1n83, A1a126 EPO.

IN THE CLAIMS:

Please amend the Claims as follows:

[[1-47]]1-52. Canceled

[[48]]53. (Previously Presented) An EPOa-hSA fusion protein, wherein the EPOa moiety is the full coding region of the human EPO sequence but wherein each amino acid residue of the EPOa moiety that serves as a site for glycosylation of the fusion protein is altered such that such a site does not serve as a site for glycosylation in the EPOa; and,

wherein both the albumin moiety and the EPOa moiety of the fusion protein is derived from a human sequence.

[[49]]54. (Previously Presented) The EPOa-hSA fusion protein of claim 48, wherein said fusion protein has the formula:

R1-L-R2; R2-L-R1; orR1-L-R2-L-R1,

wherein R1 is an erythropoietin analog amino acid sequence; L is a peptide linker and R2 is a human serum albumin amino acid sequence.

[[50]]55. (Previously Presented) The EPOa-hSA fusion protein of claim 49, wherein R1 and R2 are covalently linked via said peptide linker.

[[51]]56. (Previously Presented) The EPOa-hSA fusion protein of claim 48, wherein each amino acid residue which serves as an attachment point for glycosylation has been deleted.

[[52]]57. (Previously Presented) The EPOa-hSA fusion protein of claim 48, wherein each amino acid residue of human EPO which serves as a site for glycosylation has been replaced with an amino acid residue which does not serve as a site for

glycosylation.

[[53]]58. (Previously Presented) The EPOa-hSA fusion protein of claim 48, wherein said amino acid residue is selected from the group consisting of amino acid residues Asn24, Asn38, Asn83 and Ser126.

[[54]]59. (Previously Presented) The EPOa-hSA fusion protein of claim 48, wherein said glycosylation sites altered include Ser126, Asn24, Asn38 and Asn83.

[[55]]60. (Previously Presented) The EPOa-hSA fusion protein of claim 48, wherein said glycosylation sites altered are either O-linked or N-linked glycosylation sites and are altered by replacing an amino acid residue Asn or Ser with a Gln residue.

[[56]]61. (Previously Presented) The EPOa-hSA fusion protein of claim 48, wherein each of the amino acid residues 24, 38, 83 and 126 have been replaced with Gln.

[[57]]62. (Previously Presented) The EPOa-hSA fusion protein of claim 48, wherein each of the amino acid residues 24, 38, 83 and 126 have been deleted.

[[58]]63. (Previously Presented) The EPOa-hSA fusion protein of claim 57, wherein ~~wherein~~ each of the amino acid residues 24, 38 and 83 have been replaced with Gln and wherein said amino acid residue 126 has been replaced with Ala.

[[59]]64. (Previously Presented) The EPOa-hSA fusion protein of claim 50, wherein said peptide linker is 10 to 30 amino acids in length.

[[60]]65. (Previously Presented) The EPOa-hSA fusion protein of claim 59, wherein each of said amino acids in said peptide linker is selected from the group consisting of Gly, Ser, Asn, Thr and Ala.

[[61]]66. (Currently Amended) The EPOa-hSA fusion protein of claim 50, wherein

said peptide linker is composed of a sequence having the formula (Ser-Ser-Ser-Ser-Gly)y (SEQ ID 5) wherein y is less than or equal to 8.

[[62]]67. (Currently Amended) The EPOa-hSA fusion protein of claim 59, wherein said peptide linker is composed of either 2 or 3 tandem repeats of a sequence having the formula $((Ser\text{-}Ser\text{-}Ser\text{-}Ser\text{-}Gly)_3\text{-}Ser\text{-}Pro$ (SEQ ID 4).

[[63]]68. (Previously Presented) The EPOa-hSA fusion protein of claim 48, wherein the fusion protein includes from left to right, an EPOa which includes amino acid residues Gln24, Gln38, Gln83 and Alal26, a peptide linker, and human serum albumin.

[[64]]69. (Currently Amended) The EPOa-hSA fusion protein of claim 48, wherein the fusion protein is from left to right, Gln24, Gln38, Gln83, Ala126 EPO, a peptide linker having the formula $((Ser\text{-}Gly\text{-}Gly\text{-}Gly\text{-}Gly)_3\text{-}Ser\text{-}Pro)$ (SEQ ID 4) and human serum albumin.

[[65]]70. (Previously Presented) The EPOa-hSA fusion protein of claim 48, wherein the EPOa-hSA fusion protein includes, from left to right, human serum albumin, a peptide linker, and an EPOa which includes amino acid residues Gln24, Gln38, Gln83 and Ala126.

[[66]]71. (Previously Presented) The EPOa-hSA fusion protein of claim 65, wherein the EPOa is Gln24, Gln38, Gln83, Alal26 EPO.

[[67]]72. (Currently Amended) The EPOa-hSA fusion protein of claim 48, wherein the fusion protein is from left to right, human serum albumin, a peptide linker having the formula $((Ser\text{-}Gly\text{-}Gly\text{-}Gly\text{-}Gly)_3\text{-}Ser\text{-}Pro)$ (SEQ ID 4), and Gln24, Gln38, Gln83, Ala126 EPO.

[[68]]73. Canceled

REMARKS

The current application is a divisional of the 09/333,213 application, now issued as U.S. Patent No. 6,548,653 ("the '653 patent"). Per the Examiner's Office Action of September 19, 2005, Claims 48-67 of the current application have been allowed and are in condition for allowance except for the formal matters regarding sequence compliance which have been corrected as a result of this Reply and Amendment. After review of the file in preparation for allowance, Applicants take this opportunity to point out to the Examiner the discovery of a clerical error that occurred during the prosecution of this case. The minor error was a simple miss-numbering of the claims. So, as corrected, Claims 48-67 become Claims 53-72. No other changes are necessary and no new matter is entered. This "new" numbering sequence is provided herein. In order to clarify and validate this miss-numbering of claims for the Examiner, Applicants respectfully provide the following explanation:

The present application was filed, together with a Preliminary Amendment, on February 20, 2002. At the time of filing, Claims 1-26, 46-47 and 51-52 were pending, with Claim 52 being amended.

The Office Action issued on April 9, 2004 subjected the pending claims of this application to restriction. In response to the April 9, 2004 Restriction Requirement, Applicants elected the invention of Group I and as a result canceled the invention of Group II (Claims 51 and 52). Therefore, as a result of this response, Claims 1-26 and 46-47 were pending.

The Office Action of July 28, 2004 confirmed the pending claims of this application as Claims 1-26 and 46-47. In response to the July 28, 2004 Office Action, Applicants filed a Reply/Amendment on January 28, 2005. In this Reply, Applicants made a clerical mistake when numbering the "NEW" claims in the "Amendments to Claims" section of the Reply. As a result of this Amendment, new claims "48-68" were added – and incorrectly numbered. The new claim numbering should have started with number "53" and been numbered "Claims 53-73" (Claims 48-50 being canceled at the

time of filing and Claims 51 and 52 being canceled as a result of April 9, 2004 Restriction Requirement). Due to Applicant's miss-numbering, the Office Action of May 17, 2005 incorrectly identified the pending claims of the present application as being claims 48-68. (Applicant's Reply of August 9, 2005 then canceled then pending Claim 68). Because of Applicant's mistake, the pending/allowable claims were again miss-identified in the Office Action of September 19, 2005 as being claims 48-67, when in fact the pending claims (had they been numbered correctly in Applicant's Reply of January 28, 2005) are in fact Claims 53-72.

The above Amendments to the Claims section of this Reply amends the claim numbering in order to properly and correctly identify the pending/allowable claims of the present application. No new matter is added herein. Claims 53-72 are pending/allowable as indicated by the Examiner. Claims 48-68, as identified in Applicant's prior Replies and now re-numbered 53-72, are amended herein. No new claims are added herein. No claims are canceled herein.

Specification

The appropriate SEQ. ID. Numbers, and replacement page 3 are provided herein in compliance with the Examiner's concerns. Both a clean version of the amended page, as well as a marked up version are submitted herewith as per 37 CFR 1.125.

Drawings

The drawings filed on January 27, 2005 have been accepted by the Examiner.

Sequence Listing

Submitted herein is a paper copy of the revised Sequence Listing, as well as a diskette which contains a computer readable form of the revised Sequence Listing filed herewith. It is Applicant's understanding that the enclosed Sequence Listing complies with the requirements of 37 CFR §§ 1.821(f) and (g); and 1.824. The material on this diskette is identical in substance to the sequences appearing on noted page 3 of the amended specification. Furthermore, Applicant hereby states that the information recorded in computer readable form is identical to the written sequence listing filed

herewith as required by § 1.824(f) and does not contain any new matter as required under 37 CFR § 1.821(g).

Applicants respectfully submit that the pending claims of this application are in condition for allowance, and that this case is now in condition for allowance of all claims therein. Such action is thus respectfully requested.

If the Examiner disagrees with any of the remarks herein, or believes for any other reason that direct contact with Applicant's attorney would advance the prosecution of the case to finality, the Examiner is invited to telephone the undersigned at the number given below. Consideration of this Amendment is respectfully requested.

The Commissioner is authorized to charge any fee which may now or hereafter be due for this divisional application to GTC Biotherapeutics' Deposit Account No. 502092.

Early and favorable action is earnestly solicited.

Respectfully Submitted,

Date: 9/29/05

By: _____

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acids in the peptide linker is selected from the group consisting of (Gly, Ser, Asn, Thr and Ala; the peptide linker includes a Gly-Ser element.

In a preferred embodiment, the fusion protein includes a peptide linker and the peptide linker includes a sequence having the formula (Ser-Gly-G1y-G1y-G1y)y (SEQ. ID 1) wherein y is 1, 2,3, 4, 5, 6,7, or 8. Preferably, the peptide linker includes a sequence having the formula $(Ser\text{-}Gly\text{-}Gly\text{-}Gly\text{-}Gly)_3$ (SEQ. ID 1). Preferably, the peptide linker includes a sequence having the formula $((Ser\text{-}Gly\text{-}Gly\text{-}Gly\text{-}Gly_4\text{-}Ser\text{-}Pro)$ (SEQ. ID 3).

In a preferred embodiment, the fusion protein includes a peptide linker and the peptide linker includes a sequence having the formula (Ser-Ser-Ser-Ser-Gly)y (SEQ ID 5) wherein y is 1,2, 3, 4, 5,6, 7, or 8. Preferably, the peptide linker includes a sequence having the formula $((Ser\text{-}Ser\text{-}Ser\text{-}Ser\text{-}Gly)_3\text{-}Ser\text{-}Pro)$ (SEQ. ID 4).

In another aspect, the invention features, an EPOa-hSA fusion protein wherein the EPOa includes amino acid residues G1n24, G1n38, G1n83 and A1a126.

In a preferred embodiment the EPOa is G1n24, G1n38, Gln83, A1a126 EPO (i.e., only amino acids 24, 38, 83, and 126 differ from wild type).

In another aspect, the invention features, an EPOa-hSA fusion protein which includes from left to right, an EPOa which includes amino acid residues G1n24, Gln38, G1n83 and Ala126, a peptide linker, e.g., a peptide linker having the formula $((Ser\text{-}Gly\text{-}Gly\text{-}GIy\text{-}Gly)_4\text{-}Ser\text{-}Pro)$ (SEQ. ID 3), and human serum albumin.

In a preferred embodiment the EPOa is G1n24, G1n38, G1n83, A1a126 EPO.

In a preferred embodiment the fusion protein is from left to right, G1n24, G1n38, Gln83, Ala126 EPO, a peptide linker having the formula $((Ser\text{-}Gly\text{-}Gly\text{-}Gly\text{-}Gly)_4\text{-}Ser\text{-}Pro)$ (SEQ. ID 3), and human serum albumin.

In another aspect, the invention features, an EPOa-hSA fusion protein which includes, from left to right, human serum albumin, a peptide linker, e.g., a peptide linker having the formula $((Ser\text{-}Gly\text{-}Gly\text{-}Gly\text{-}Gly)_{34}\text{-}Ser\text{-}Pro)$ (SEQ. ID 3), and an EPOa which includes amino acid residues G1n24, G1n38, G1n83 and Ala126.

In a preferred embodiment the EPOa is G1n24, G1n38, Gln83, Ala126 EPO.

In a preferred embodiment the fusion protein is from left to right, human serum albumin, a peptide linker having the formula $((Ser\text{-}Gly\text{-}G1y\text{-}GIy\text{-}Gly)_4\text{-}Ser\text{-}Pro)$ (SEQ. ID 3), and Gln24, Gln38, G1n83, A1a126 EPO.

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

Applicant: **Meade et al.** Art Unit No.: **1632**

Application No.: **10/081,400** Examiner: **Joseph T. Woitach**

Filed: **February 20, 2002**

For: **ERYTHROPOIETIN ANALOG-HUMAN SERUM ALBUMIN FUSION**

Attorney Docket Number: **GTC-6D**

Mail Stop AF
Commissioner for Patents
P.O. Box 1450
Alexandria, VA 22313-1450

AMENDMENT AFTER FINAL AND TRANSMITTAL OF SEQUENCE LISTING

Enclosed is a diskette which contains a computer readable form of the revised Sequence Listing filed herewith. It is Applicant's understanding that the Sequence Listing complies with the requirements of 37 CFR §§ 1.821(f) and (g); and 1.824. The material on this diskette is identical in substance to the sequences appearing or noted on page 3 of the amended specification which is submitted herewith. Furthermore, Applicant hereby states that the information recorded in computer readable form is identical to the written sequence listing filed herewith as required by § 1.824(f) and does not contain any new matter as required under 37 CFR § 1.821(g).

Respectfully Submitted,

Date: 9/29/05

By: _____
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ATTORNEY FOR APPLICANTS
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CERTIFICATE OF MAILING UNDER 37 CFR 1.8

I hereby certify that this correspondence is being deposited on 9/29/05 with the United States Postal Service as first class mail with sufficient postage on the date indicated above and is addressed to: Mail Stop AF, Commissioner for Patents, P.O. Box 1450, Alexandria, VA 22313-1450.

_____
Dawn C. Greenaway

SEQUENCE LISTING

<110> Young, Michael
Meade, Harry
Krane, Ian

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